International Journal of Phytopharmacy
Vol. 4 (2), pp.37-43, Mar-Apr 2014
ISSN: 2277-2928 (Online)
Journal DOI:10.7439/ijpp

www.ssjournals.com

Review Article

Current status of natural products for the treatment of liver disease-A review

Sabeena Hussain Syed and Ajay Gajanan Namdeo*

Department of Pharmacognosy, Poona College of Pharmacy, Bharati Vidyapeeth Deemed University Pune- 411038

***Correspondence Info:**
Dr. Ajay Gajanan Namdeo
Dept of Pharmacognosy,
Poona College of Pharmacy,
Bharati Vidyapeeth Deemed University, Erandwane, Pune, India-411 038
E-Mail: agnamdeo@gmail.com

Abstract

Liver disease, also known as hepatic disease is any condition that may cause disturbance of liver function and causes illness. The liver is responsible for many vital functions within the body and should it become diseased or injured, the loss of those functions can cause significant damage to the body. Natural products which are derived from plant extracts, herbs, animals, marine and microbes are used traditionally for treatment of liver ailments. More than 50% of the drugs on the market are still based on natural products. That means, natural products serve as lead structure, providing the "idea" for a new drug. The present work constitutes a review of the literature on natural products from plants, marine and microbiological sources for the treatment of liver diseases. This work intends to aid researchers in the study of natural products useful in alleviating liver disorders.
Keywords: liver diseases, herbs, marine, natural products

1. Introduction

Liver, the most important organ of human body involved in metabolism, synthesis, excretion and detoxification of various endogenous and exogenous substances such as drugs. Such physiological activity of the liver results in the production of highly reactive species known as free radicals. These highly unstable free radicals combine with the membrane lipids by covalent bond results in the alteration of membrane permeability of hepatic cells leading to tissue damage[1]. Liver disease afflicts over 10% of the world population. This constitutes hepatitis, cirrhosis, fibrosis, hepatic steatosis (fatty liver) alcoholic liver disease and drug induced liver disease[2]. Morbidity and mortality resulting from liver diseases is a major public health problem worldwide especially in developing countries.

The management of liver disease is still a challenge to modern medicine as there is no effective drug available that stimulates liver function, offer protection to the liver from damage or help to regenerate hepatic cells. The only drugs available are Corticosteroids and Immunosuppressive agents. However, these suffer with several adverse effects. It is therefore necessary to search for alternative drugs for the treatment of liver diseases to replace currently used drugs of doubtful efficacy and safety[3].

In the present day scenario, nearly half of the agents used in liver diseases are either natural products or derivatives of natural products due to their ability to act on various biological targets, so there remains a great interest in the search for natural products from plants, terrestrial and marine animals and microorganisms as potential drug chemical leads for the treatment of a liver disease. Among the wide range of natural sources, herbal source play a key role, where 65% of patients in US and Europe depend on herbal preparations for the treatment of liver diseases[2]. The aim of the present review is to summarize the available experimental findings regarding natural sources (herbal, marine and microbiological) used to treat liver diseases and their underlying mechanism.

2. Methodology

Relevant published studies were identified for the years 2003-2013 by means of Elsevier-Science direct, Pubmed and Google scholar. The search included in terms of following keywords: "plants", "plant extracts", "marine", "fermented products", which are cross-referenced with the keywords: "liver diseases", "hepatoprotective", "hepatoprotective activity" and "anti-hepatotoxic". The articles founded were studied for the details on models used for testing the activity along with their mechanism of action.

3. Herbal medicines for the treatment of liver diseases

Herbal medicines have been used to treat liver disorders for thousands of years and have now become a promising therapy for various pathological liver conditions. In India, over 40 polyherbal commercial formulations reported to have hepatoprotective action are being used along with 160 phytoconstituents from 101 plant families[4,5]. A list of plants reported to have significant hepatoprotective activity is shown in Table 1 in alphabetical order of the plant scientific name together with the part of the plant used, kind of extract used or compound isolated, including model, type of assay and mechanism of action involved.

Han *et al*[6] reported the hepatoprotective activity of *Artemisia capillaris* aqueous extract against bile duct ligation induced liver damage. The elevated serum enzyme levels and antioxidant parameters were restored by the extract. The extract also attenuated the levels of

alpha smooth muscle action (α-SMA) due to bile duct ligation. Results of the study indicates that *Artemisia capillaris* can be used as anti-hepato fibrotic remedy, especially in chloestatic liver disorder and the responsible mechanism may involve the regulation of oxidative stress-associated enzymes and fibrogenic cytokines. The constituents identified in the aqueous extract by UPLC-MS analysis are 3,4,5-cafeoyl quinic acid and quercetin.

Eugenia jambolana (Jamun) is a berry fruit, used in traditional medicine such as Ayurveda for various ailments. Ajay *et al*[7] reported anthocyanin derivatives present in jamun fruit extract probably elicit hepatoprotective activity through attenuating NF-kB signalling, inflammation and oxidative stress, macrophage accumulation and lipid peroxidation. The hepatoprotective activity by carotenoids in isoniazid-rifampicin induced hepatic injury in rats has been reported[8]. Carotenoids effectively inhibited the lipid peroxidation and enhanced the anti-oxidant enzyme system which may be responsible for its hepatoprotective action. Chanchal *et al*[9] investigated the hepatoprotective activity of *Psidium guajava* aqueous leaf extract against CCl_4, thioacetamide and paracetamol induced liver injury. In chronic liver injury induced by CCl_4 the *P. guajava* leaf extract reduced the elevated serum enzyme levels. The hepatoprotective activity of the plant may be due to antioxidant effect of the plant.

Ku *et al*[10] reported the hepatoprotective effect of *Cirsium arisanense* Kitamura in tacrine treated hepatoma hep 3B cells and C57BL mice. Phenol containing aqueous components of *C. arisanense* roots exhibited higher phenolic content and antioxidant capacity than leaves and hepatoprotective action of roots occurs via increase in glutathione levels and elimination of the nitric oxide production.

Table 1: Herbs with their representative extract/ single compound investigated for prevention of liver diseases

Plant Name (Family)	Part of the plant	Extract/Compound	Pharmacological Model	Type of study	Mechanism	Reference
Acacia auriculiformis (Fabaceae)	Bark and empty pods	70% acetone extract	Paracetamol induced	*In-vivo*	Antioxidant:↑CAT,GSH, GP_X,SOD	Sathya *et al*[11]
Acacia confuse (Fabaceae)	Bark	Ethanol extract/Gallic acid	CCl_4 induced	*In-vivo*	Antioxidant: ↑CAT, GPx, ↓MDA, CYP2E1	Tung *et al*[12]
Aralia continentalis (Araleaceae)	Root	70% ethanol water extract	CCl_4 induced	*In-vivo*	Antioxidant: ↑GSH, GST, HO-1 ↓MDA	Hwang *et al*[13]
Barleria prinotis (Acanthaceae)	Leaves and stems	Ethylacetate extract/iridoid glycosides	Paracetamol/ CCl_4 /D-GalN induced	*In-vivo*	Antioxidant: ↑GSH, ↓LPO	Singh *et al*[14]
Camelia oleifera (Theaceae)	Seed	Seed oil	CCl_4 induced	*In-vivo*	Antioxidant: ↑GSH, GST, GR	Lee *et al*[15]
Carthamus tictorus (Asteraceae)	Flowers	Carthamus red	CCl_4 induced	*In-vivo*	Antioxidant: ↑CAT,GSH, SOD	Shuang *et al*[16]
Dendrobium huoshanense (Orchidaceae)	Stem	Galactoglucomannan	Selenium induced	*In-vivo*	Antioxidant: ↑CAT, GSH, SOD Antifibrinolytic: ↓ TGF-β1,	Pan *et al*[17]
Elephantopus scaber (Asteraceae)	Roots	Deoxyelephantopin (sesquiterpene lactone)	D-GalN/LPS induced	*In-vivo*	Antiinflammation ↓TNF-α	Huang *et al*[18]
Enicostemma axillare (Gentianaceae)	Whole plant	Swertiamarin	CCl_4 induced	*In-vivo*	Antioxidant: ↑CAT, GSH, SOD, ↓LPO	Jaishree *et al*[19]
Eucommia ulmoides (Eucommiaceae)	Leaves	Aqueous extract/ protocatechuic acid	CCl_4 induced	*In-vivo*	Antioxidant:↑GSH,GPx,GST↓MDA	Hung *et al*[20]
Fumaria indica (Fumariaceae)	Whole plant	Butanol extract/protopine	D-Gal N induced	*In-vivo*	Antioxidant:↑GSH,↓LPO	Rathi *et al*[21]
Fumaria Parvifolia (Fumariaceae)	Whole plant	50%ethanol extract/fumaricacid and protopine	Nimesulide induced	*In-vitro*	Anti-apoptotic: ↑Bcl-2/Bax ratio, ↓cytochrome C, ↓caspase-9/3activation,	Tripathi *et al*[22]
Gentiana scabra (Gentianaceae)	Rhizomes	Aqueous extract/polyphenols	CCl_4 induced	*In-vivo*	Antioxidant: ↑CAT, GPx, SOD.	KO *et al*[23]
Indigofera tinctoria (Leguminosae)	Aerial parts	Trans-teracos-15-enoic acid	CCl_4 induced	*In-vivo*	Antioxidant: ↑GSH ↓MDA	Singh *et al*[24]
Laggera alata (Asteraceae)	Whole plant	Aqueous extract/isocholorogenic acid	D-GalN induced	*In-vitro*	AntihepatitisB: ↓translation of HBV virus by ↑ HO-1 expression	Hao *et al*[25]
Launea procumbens (Asteraceae)	Aerial parts	Chloroform extract/phenolic compounds	CCl_4 induced	*In-vivo*	Antioxidant: ↑CAT, GSH, SOD,GP_X	Khan *et al*[26]
Luffa acutangula (Cucurbitaceae`)	Fruits	Hydroalcoholic extract	CCl_4 and rifampicin induced	*In-vivo*	Antioxidant: ↑CAT, GSH, SOD, ↓MDA	Jadhav *et al*[27]
Lycium chinensis (Solanaceae)	Fruits	Aqueous extract	CCl_4 induced	*In-vivo*	Antioxidant: ↑GSH, ↓MDA CYP2E1	Ha *et al*[28]
Moringa oleifera (Moringceae)	Seeds	Ethanolic extract	CCl_4 induced	*In-vivo*	Antifibrinolytic: ↓α-SMA, Collagens I and III Antioxidant: ↑CAT SOD, ↓MDA	Hamza *et al*[29]
Murraya Koenigii (Rutaceae)	Leaves	Aqueous extract/carbazole alkaloid and tannins	Ethanol induced	*In-vitro*	Antioxidant: ↑CAT, GSH, SOD. ↓LPO	Sathaye *et al*[30]
Perilla frutscens (Lamiaceae)	Leaves	Aqueous extract/ Caffeic acid, Rosmarinic acid	t-BHP induced	In-vivo	Antioxidant: ↑CAT,GSH, GP_X,SOD↓LPO	Yang *et al*[31]
Platycodon	Root	Aqueous	CCl_4 induced	*In-vivo*	Anti-apoptotic: ↓caspase-	Lee *et al*[32]

grandiflorum (Companulaceae)		extract/saponin fraction			9/3activation Antioxidant:↑GSH,↓CYP2E1	
Sida Cordata (Malvaceae)	Leaves	Ethanol extract	CCl_4 induced	*In-vivo*	Antioxidant: ↑CAT,GSH,SOD, ↓LPO	Sunil *et al*[33]
Sphaeranthus amaranthoides (Asteraceae)	Whole plant	Ethanolic extract	D-GalN induced	*In-vivo*	Antioxidant:↑CAT, GSH,GP_X,GR,G6PD,SOD	Swarnalatha *et al*[34]
Symplocus racemosa (Symplocaceae)	Bark	Ethanol extract	CCl_4 induced	*In-vivo*	Antioxidant: ↑CAT, GSH, SOD, ↓MDA	Dhananjay *et al*[35]
Terminalia catappa (Combretaceae)	Leaves	Aqueous extract/Corilagin	D-GalN/LPS induced	*In-vivo*	Antiapoptotic:↓caspase-9/3activation Antioxidant: ↑GST	Kinoshita *et al*[36]
Urtica dioca (Utricaceae)	Seed	Diethyl ether extract	Aflatoxin induced	*In-vivo*	Antioxidant: ↑CAT,SOD ↓MDA	Yener *et al*[37]
Woodfordia fruticosa (Lythraceae	Flowers	Methanolic extract	Thioacetamide induced	*In-vivo*	Antioxidant: ↑CAT, GSH, SOD,GP_X	Nitha *et al*[38]

4. Phytoconstituents as hepatoprotective agents

Antioxidant and hepatoprotective activities of flavonoids, polyphenols, terpenoids and phenyl propanoids are well explored. A list of these compounds is shown in Table 2 with information on the chemical nature, class of compound and its mechanism of action.

Ahmed *et al*[39] investigated the hepatoprotective activity of cichotyboside, a sesquiterpene glycoside obtained from the seeds of *Cichorium intybus*. Cichotyboside attenuated the levels of serum enzyme markers which were elevated due to CCl_4 intoxication. Two new oleanolic acid saponins celosin C and celosin D were isolated from the ethanol extract of *Semen celosiae* which were investigated for hepatoprotective action against CCl_4 induced toxicity[40]. Isolated saponins showed prophylaxis action which was evident from restoring the serum biochemical and antioxidant parameters.

Troxerutin, a trihydroxyethylated derivative of rutin protects the mouse liver against oxidative stress mediated injury induced by D-galactosamine[41]. Troxerutin protected the mouse liver by attenuating lipid peroxidation, renewing the activities of antioxidant enzymes and suppressing inflammatory response. Oh *et al*[42] reported the hepatoprotective activity of onitin and luteolin isolated from the aerial parts of *Equisetum arvense* against tacrine induced cytotoxicity in human liver derived Hep G2 cells. The presences of antioxidant principles in plant are responsible for its hepatoprotective action.

Table 2: Chemically defined molecules with hepatoprotective action

Phytocompound	Pharmacological Model	Typeof study	Mechanism	References
α &β amyrin Triterpene)	Acetaminophen induced	*In-vivo*	Antioxidant: ↑GSH	Oliveria *et al*[43]
Arjunolic acid (Triterpenoid saponin)	Paracetamol induced	*In-vivo*	Antiapoptotic:↓phosphorylations of JNK/Bcl-2	Ghosh *et al*[44]
Asiaticoside (Triterpenoid)	D-GalN/LPS induced	*In-vivo*	Anti-inflammatory: ↓ TNF- α	Zhang *et al*[45]
Baicalein (Flavone)	D-GalN/LPS induced	*In-vivo*	Antiapoptotic: ↑Bcl-2/Bax ratio, ↓cytochrome C	Wu *et al*[46]
Berberine (Isoquinoline alkaloid)	H_2O_2-induced	*In-vitro*	Antiapoptotic: ↑sirtuin1	Zhu *et al*[47]
Chrysin (Flavone)	N-nitrosodiethylamaine induced	*In-vivo*	Antioxidant: ↓MDA,NO Antihepatocarcinogenic:↓PCNA	Glory *et al*[48]
Curcumin (Polyphenol)	Dimethylnitrosamine induced	*In-vivo*	Anti-inflammatory: ↑Nrf2,HO-1	Farombi *et al*[49]
Dehydrocavidine (Alkaloid)	CCl_4 induced	*In-vivo*	Antioxidant: ↑CAT, GPx, SOD. ↓LPO Antifibrinolytic: ↑collagenolysis	Wang *et al*[50]
Echinacoside (Phenyl ethanoid)	CCl_4 induced	*In-vivo*	Antioxidant:↑GSH SOD. ↓MDA	Wu *et al*[51]
Genipin (Aglycone)	D-GalN/LPS induced	*In-vivo*	Antioxidant: ↑GSH Antiapoptotic:↓caspase-9/3activation, ↓cytochrome C	Kim *et al*[52]
Genistein (Isoflavone)	Acetaminophen induced	*In-vivo*	↑UDP-glucuronosyltransferase Antioxidant:↑ GP_X, ↓CYP2E1	Jing *et al*[53]
Hesperitin (Flavanone)	Cadmium induced	*In-vivo*	Antioxidant:↑CAT,GSH, GP_X,SOD	Pari *et al*[54]
Kahweol / Cafestol (Diterpenes)	CCl_4 induced	*In-vivo*	Antioxidant: ↓CYP2E1	Lee *et al*[15]
Kolaviron (Flavanoid)	Dimethylnitrosamine induced	*In-vivo*	Antioxidant: ↑ GSH ↓MDA Anti-inflammatory:↓COX-2 and Inos	Farombi *et al*[55]
Lupeol (Triterpene)	Acetaminophen induced	*In-vivo*	Antioxidant:↑GSH,SOD Antiapoptotic: ↑Bcl-2/Bax ratio, ↓caspase-9/3 activation	Kumari *et al*[56]
Mangiferin (Phenol)	D-GalN induced	*In-vivo/In-vitro*	Antioxidant: ↑Nrf2,HO1,GST-α Antiinflammation: ↓TNF,IFN-γ	Das *et al*[57]
Oleuropein (Secoiridoid)	CCl_4 induced	*In-vivo*	Antioxidant: ↑SOD, GSH Antifibrinolytic:↓HSC activation Antiinflammatory:↑HO-1 expression ↓ TNF- α	Domitrovic *et al*[58]
Phyllanthin (Lignan)	Ethanol induced	*In-vitro*	Antioxidant:↑GR, GSH, SOD	Chirdchupanseree *et al*[59]
Puerarin (Isoflavone)	CCl_4 induced	*In-vivo*	Antioxidant:↑CAT,GSH, GP_X,SOD ↓LPO	Xia *et al*[60]
Schisandrin B (Lignan)	CCl_4 induced	*In-vivo*	Antioxidant: ↑GSH, GPx, GST, SOD, HSP 25/70 ↓MDA	Chiu *et al*[61]
Ursodeoxycholic acid	Alcoholic induced	*In-vivo*	Antioxidant:↑GSH,SOD ↓MDA	Lukivskaya *et al*[62]
Xanthohumol (Prenyl flavonoid)	CCl_4 induced	*In-vivo*	Antioxidant: ↑CAT, GSH, SOD. ↓LPO	Pinto *et al*[63]

5. Marine sources for treatment of liver diseases.

Recently much attention has been given to marine organisms due to their considerable biodiversity that has been found in the widespread oceans that cover over 70% of the world. Structurally unique secondary metabolites have been isolated and identified from marine organisms which are reported for their anti-cancer, anti-bacterial, anti-inflammatory and anti-hypertensive actions[64]. Some marine sources with established hepatoprotective activity are shown in Table 3 with information on type of marine source, and their mechanism of action.

Table 3: Marine sources with reported hepatoprotective action

Marine Source	Type of organism	Extract/Compound	Model	Type of study	Mechanism	Reference
Chlorella vulgaris	Green algae	Aqueous extract	CCl_4 induced	*In-vivo*	Antioxidant:↑CAT,SOD,GSH,GST	Li *et al*[65]
Dunaliella salina	Green algae	Carotenoid rich	CCl_4 induced	*In-vivo*	Antioxidant:↑CAT,SOD,GSH,GPx↓MDA	Hsu *et al*[66]
Ecklonia stolonifera	Brown algae	Phlorofucofureckol A	Tacrine induced	*In-vitro*	Antiapoptotic: ↓ROS, JNK phosphorylation	Lee *et al*[67]
Gelonia eros	Hard clam (Mollusk)	Ethylacetate	CCl_4 induced	*In-vivo*	Antioxidant:↑SOD,GSH,GPx↓MDA	Yeh *et al*[68]
Hizikia fusiformis	Brown algae	Glycoprotein	Acetaminophen induced	*In-vivo*	Antiapoptic: ↓caspase-9/3activation	Hwang *et al*[6]
Holothuria alra	Sea cucumber	Acetonitrile/trifluroacetic acid-60:40	Thioacetamide induced	*In-vivo*	Antioxidant:↑CAT,SOD,GSH,GPx↓MDA	Esmat *et al*[70]
Hypnea muciformis	Red algae	Ethanolic extract	CCl_4 induced	*In-vivo*	Antioxidant: ↓LPO	Bupesh *et al*[71]
Padina boergesenii	Brown algae	Diethylether	CCl_4 induced	*In-vivo*	Antioxidant:↑CAT,SOD,GPx↓LPO	Karthikeyan *et al*[72]
Sargassum polycystum	Brown sea weed	Ethanolic extract	Paracetamol induced	*In-vivo*	Antioxidant: ↑thiols level	Raghvendran *et al*[73]

6. Microbiological sources as hepatoprotectants

Microorganisms being a productive source of structurally diverse bioactive metabolites have yielded some of the most important products of pharmaceutical industry. These include antibacterial, immunosuppressive, cholesterol lowering and antitumor antibacterial agents. Table 4 enlisted the microbial sources for the treatment of liver diseases along with their type of study and mechanism of action.

Table 4: Biological sources and their activity against liver hepatotoxins

Organism	Type of organism	Extract/ compound	Pharmacological Model	Type of Study	Mechanism	Reference
Antrodia cinnamomea	Mushroom	Ethanol extract/antroquinonol	Ethanol induced	*In-vivo/ in-vitro*	Antioxidant:↑GSH ↓LPO,ROS	Kumar *et al*[74]
Arthrospria platensis	Cyanobacterium	P-Phycocyanin	CCl_4 induced	*In-vivo*	Antioxidant:↑CAT,GP_X GR,SOD	Nagaraj *et al*[75]
Cordyceps militaris	Fungi	Aqueous extract	t-BHP induced	*In-vitro*	Antiapoptotic : Anti-apoptotic: Bcl-2/Bax ratio, ↓caspase-3-activity	Wang *et al*[76]
Ganoderma lucidum	Lingzhi mushroom	Ganodermanondiol	t-BHP induced	*In-vitro*	Antioxidant:↑GSH, HO-1	Li *et al*[77]
Ganoderma tsuage	Reishi Mushroom	Aqueous extract	CCl_4 induced	*In-vivo*	Antifibrotic:↓prothrombin time	Wu *et al*[78]
Monascus anka	Mold	Dimerumic acid	CCl_4 induced	*In-vivo*	Antioxidant:↑CAT,GSH,SOD	Aniya *et al*[79]
Morchella esculenta	Morel mushroom	Cultured mycelium	Ethanol & CCl_4 induced	*In-vivo*	Antioxidant:↑CAT,GSH,GST GP_X,SOD	Nitha *et al*[80]
Phormidium tenue	Cyanobacterium	Phycoerythrin	CCl_4 induced	*In-vivo*	Antioxidant:↑CAT,GSH,SOD ↓MDA	Soni *et al*[81]
Pleurotus ostreatus	Oyster mushroom	Ethanol extract	CCl_4 induced	*In-vivo*	Antioxidant:↑CAT,GSH,SOD	Jayakumar *et al*[82]
Sacchromyces cerevisiae (YA03083)	Baker's yeast	Fermented extract containing GSH, Cysteine	CCl_4 induced	*In-vivo*	Antifibrogenetic:↓hydroxyproline, Collagenα1(I),TGF-β1	Lai *et al*[83]
Spirulina platensis	Cyanobacterium	Phycocyanin	Mercuric chloride induced	*In-vivo*	Antioxidant:↑GSH ↓MDA	Bashandy *et al*[84]

7. Conclusion

The present study reveals the laboratory findings of plant extracts and their isolated compounds, marine and microbial findings for the treatment of liver disease, highlighting on natural products that harbour bioactive molecules which may exert hepatoprotective action. Natural products have traditionally favored the identification and investigation of potential targets for drug development and this function is still of importance today. The pharmaceutical industry is facing serious challenges as the drug discovery process is becoming extremely expensive, riskier and critically inefficient. Natural products have served as a major source of drugs for centuries, and about half of the pharmaceuticals in use today are derived from natural products. However careful experimental designs using multidisciplinary approaches along with standardization and characterization of natural products are critical for the successful development of novel and promising therapies.

Acknowledgements

The authors acknowledge the grants received from University Grants Commission (UGC) for this project under Maulana Azad National Fellowship (MANF) Scheme. F1-17.1/2010/MANF-MUS-AND-4007 / (SA-III/Website).

References

1. Kohen, R., Nyska A. Oxidation of biological systems: oxidative stress phenomena, antioxidants, redox reactions and methods for their quantification. *Toxicol Pathol*. 2002; 30: 620-650.
2. Zhang, A., Sun, H., Wang, X. Recent advances in natural products from plants for treatment of liver diseases. *Eur J Med Chem*. 2013; 63: 570-77.
3. Adewusi, E.A., Afolayan, A.J. A review of natural products with hepatoprotective activity. *J Med Plant Res*. 2010; 4: 1318-1334.
4. Handa, S.S., Sharma, A., Chakraborti. Natural products and plants as liver protecting drugs. *Fitoterapi*a. 1986; 57: 307-49.
5. Sharma, A., Singh R.T., Sehgal V., Handa S.S. Anti-hepatotoxic activity of some plants used in herbal formulations. *Fitoterapia*. 1991; 62: 131-138.
6. Han, J.M., Kim, H.G., Choi M.K., Lee, J.S., Lee, J.S., Wang,J.H., et al. *Artemisia capillaris* extract protects against bile duct ligation-induced liver fibrosis in rats. *Exp Toxicol Pathol*.2013; 65: 837-844.
7. Ajay, C.D., Aleksunes, L.M., Driscoll, M.V., Seeram, N.P., Slitt, A.L. The traditional ayurvedic medicine, *Eugenia jambolana* (Jamun fruit), decreases liver inflammation, injury and fibrosis during cholestasis. *Liver Int*. 2010; DOI:10.1111/j.1478-3231.2011.02724.x.
8. Rana, S.V., Pal, R., Vaiphei, K., Ola, R.P., Singh, K. Hepatoprotection by carotenoids in isoniazid–rifampicin induced hepatic injury in rats. Biochem. *Cell Biol*.2010; 88: 819–834.
9. Chanchal, K.R., Jagadish, V.K., Asad, M. Hepatoprotective activity of *Psidium guajava* Linn. leaf extract. *Ind J Exp Biol*. 2006; 44: 305-311.
10. Ku KL1, Tsai CT, Chang WM, Shen ML, Wu CT, Liao HF. Hepatoprotective effect of *Cirsium arisanense* Kitamura in tacrine-treated hepatoma Hep 3B cells and C57BL mice. *Am J Chin Med*. 2008; 36(2):355-68.
11. Sathya, A., Siddhuraju P. Protective effect of bark and empty pod extracts for *Acacia auriculiformis* against paracetamol intoxicated liver injury and alloxan induced type II diabetes. *Food Chem Toxicol*. 2013; 56: 162-170.
12. Tung, Y.T., Wu, J.H., Huang, C.C., Peng, H.C., Chen, Y.L., Yang, S.C., et al. Protective effect of *Acacia confusa* bark extract and its active compound gallic acid against carbontetrachloride induced chronic liver injury in rats. *Food Chem Toxicol*. 2009; 47: 1385-1392.
13. Hwang, Y.P., Choi, J.H., Jeong, H.G. Protective effect of the *Aralia continentalis* root against carbontetrachloride induced hepatotoxicity in mice. *Food Chem Toxicol*. 2009; 47: 75-81.
14. Singh, B., Chandan, B.K., Prabhakar, A., Taneja, S.C., Singh, J., Qazi, G.N. Chemistry and hepatoprotective activity of an active fraction from *Barleria prinotis* Linn in experimental animals. *Phytother Res*. 2005; 19: 391-404.
15. Lee, C.P., Shin, P.H., Hsu, C.L., Yen, G.C. Hepatoprotection of tea seed oil (*Camelia oleifera* Abel) against CCl_4 induced oxidative damage. *Food Chem Toxicol*. 2007; 45: 888-895.
16. Shuang Lu, Wang Quan, Shao-Ming Wang, Hong-Ling Liu, Yong Tan, Guang-Ping Zeng, Xia Zhang. Correlation of soil microbes and soil micro-environment under long-term safflower (*Carthamus tinctorius* L.) plantation in China. *J Environ Biol* 2013 Apr; 34(2 Spec No):471-9.
17. Pan, L.H., Lu, J., Luo, J.P., Zha, X.Q., Wang, J.H. Preventive effect of a galactoglucomannan (GGM) from *Dendrobium huoshanense* on selenium induced liver injury and fibrosis in rats. *Exp Toxicol Pathol*. 2012; 64: 899-904.
18. Huang,C.C., Lin, K.J., Cheng, Y.W., Hsu, C.A., Yang, S.S., Shyur L.F. Hepatoprotective effect and mechanistic insights of deoxyelephantopin, a phyto-sesquiterpene lactone, against fluminant hepatitis. *J Nutr Biochem*. 2013; 24: 516-530.
19. Jaishree, V., Shrishilappa B, Praveen, T.K. Antioxidant and hepatoprotective effect of ethylacetate extract of *Enicostemma axillare* (Lam) Raynal against CCl_4 induced liver injury in rats. *Indian J Exp Biol*. 2010; 48; 896-904.
20. Hung, M.Y., Fu, T.Y., Shih, P.H., Lee, C.P., Yen, G.C. Du-Zhong (*Eucommia ulmoides* Oliv) leaves exhibits CCl_4 induced hepatic damage in rats. *Food Chem Toxicol*. 2006; 44: 1424-1431.
21. Rathi, A., Arvind Kumar, S., Annie, S., Ajay Kumar, S.R., Shanta M. Hepatoprotective potentials of *Fumaria indica* Pugsley whole plant extracts, fractions, an isolated alkaloid protopine. *Phytomed*. 2008; 15: 470-477.
22. Tripathi Madhulika, Singh Brijesh Kumar , Mishra Chetna , Sheikh Raisuddin, Kakkar Poonam. Involvement of mitochondria mediated pathways in hepatoprotection conferred by *Fumaria parviflora* Lam. extract against nimesulide induced apoptosis *in vitro*. *Toxicol In Vitro* 2010 Mar 20; 24(2):495-508.
23. Ko, H.J., Chen, J.H., Ng, L.T., Hepatoprotection of *Gentiana scabra* extract and polyphenols in liver of carbontetrachloride intoxicated mice. *J Enivron Pathol Toxicol Oncoll*. 2011; 30: 179-187.
24. Singh, B., Chandan, B.K., Sharma, N., Bhardwaj, V., Satti, N.K., Gupta, V.N. Isolation, structure elucidation and in-vivo hepatoprotective potential of trans-tetracos-15-enoic acid from *Indigofera tinctora* Linn. *Phytother. Res*. 2006; 20: 831-839.
25. Hao, B.J., Wu, Y.H., Wang, J.G., Hu, S,Q., Keil, D.J., Hu, H.J., et al. Hepatoprotective and antiviral properties of isochlorogenic acid A from *Laggera alata* against hepatitis B virus infection. *J Ethnopharmacol*. 2012; 144: 190-194.
26. Khan, R.A., Khan, M.R., Mushtaq, A., Sahreen, S., Shah, N.A. Hepatoprotection with a chloroform extract of *Launea procumbens* against CCl_4 induced injuries in rats. *BMC Complement Altern Med*. 2012; 12: 114-125.
27. Jadhav, V.B., Thakare, V.N., Suralkar, A.A., Deshpande A,D., Naik, S.R. Hepatoprotective activity of *Luffa actangula* against CCl_4 and rifampicin induced liver toxicity in rats: Biochemical and histopathological evaluation. *Indian J Exp Biol*. 2010; 48: 822-829.
28. Ha, K.T., Yoon, S.J., Choi, D.Y., Kim, D.W., Kim, J.K., et al. Protective effect of *Lycium chinense* fruit on carbontetrachloride induced hepatotoxicity. *J Ethnopharmcol*. 2005; 96: 529-535.
29. Hamza, A.A. Ameliorative effects of *Moringa oleifera* Lam seed extract on liver fibrosis in rats. *Food Chem Toxicol*. 2010; 48: 345-355.
30. Sathaye, S., Bagul, Y., Gupta, S., Kaur, H., Redkar, R. Hepatoprotective effects of aqueous leaf extract and crude isolates of *Murraya koenigii* against *in-vitro* ethanol induced hepatotoxicity model. *Exp Toxicol Pathol*. 2011; 63: 587-591.
31. Yang, S.Y., Hong, C.O., Lee, G.P., Kim, C.T., Lee, K.W. Protective effect of saponins derived from the roots of *Platycodon grandiflorum* against carbontetrachloride induced hepatotoxicity in mice. *Food Chem Toxicol*. 2013; 46: 1778-1785.
32. Lee, K.J., Choi, J.H., Jeong, H.G. Hepatoprotective and antioxidant effects of the coffee diterpenes kahweol and cafestol on carbon tetrachloride-induced liver damage in mice. *Food Chem Toxicol*. 2007; 45: 2118–2125.
33. Sunil, M., Dutt, K.R., Jena, J. Protective effect of *Sida cordata* leaf extract against CCl_4 induced acute liver toxicity in rats. *Asian Pac J Trop* Med. 2013; 280-284.
34. Swarnalatha, L., Neelakanta Reddy, P. Hepatoprotective activity of *Sphaeranthus amaranthoides* on D-galactosamine induced hepatitis in albino rats. *Asian Pac J Trop Biomed*. 2012; S1900-1905.
35. Dhananjay, W., Dilpesh, J., Abhay, S., Rahul, S. Hepatoprotective activity of *Symplocos racemosa* bark on carbontetrachloride induced hepatic damage in rats. *J Ayur Inte Med*. 2011; 2: 137-143.
36. Kinoshita, S., Inoue, Y., Nakama, S., Ichiba, T., Aniya, Y. Antioxidant and hepatoprotective actions of medicinal herb, *Terminalia catappa* from Okinawa island and its tannin corilagin. *Phytomed*. 2007; 14: 755-762.
37. Yener, Z., Celik, I., Ilhan, F., Ramazan B. Effects of *Urtica dioica* L. seeds on lipid peroxidation, antioxidants and liver pathology in aflatoxin induced tissue injury in rats. *Food Chem Toxicol*. 2009; 47: 418-424.

38. Nitha, A., Ansil, P.N., Prabha, S.P., Wills, P.J., Latha, M.S. Preventive and curative effect of *Woodfordia fruticosa* kurz flowers on thioacetamide induced oxidative stress in rats. *Asian Pac J Trop Biomed*. 2012; S757-764.
39. Ahmed, B., Khan, S., Masood, M.H., Siddique, AH. Anti-hepatotoxic activity of cichotyboside, a sesquiterpene glycoside from the seeds of *Cichorium intybus*. *J Asian Nat Prod Res*. 2008; 10: 223-231.
40. Sun, Z.L., Wang, Y., Guo, M.L., Li, Y.X. Two new hepatoprotective saponins from *Semen celosiae*. *Fitoterapia*. 2010; 81: 375-380.
41. Zhang, Z.F., Fan SH, Zheng YL, Lu J, Wu DM, Shan Q, et al. Troxerutin protects the mouse liver against oxidative stress-mediated injury induced by D-galactose. *J. Agric Food Chem*.2009; 57: 7731-7736.
42. Oh, H., Kim, OH., Cho JH., Kim, YC. Hepatoprotective and free radical scavenging activities of phenolic petrosins and flavonoids isolated from *Equistem arvense*. *J Ethnophrmcol*. 2004; 95: 421-424.
43. Oliveira, F.A., Chaves, M.H., Almeda, F.R.C., Lima, R.C.P., Silva, R.M., Maia, J.L., et al. Protective effect of α and β-amyrin, a triterpene mixture from *Protium heptaphyllum* trunk wood resin, against acetaminophen-induced liver injury in mice. *J Ethnopharmacol*. 2005; 98, 103-108.
44. Ghosh, J., Das, J., Manna, P., Sil, P.C. Protective effect of the fruits of *Terminalia arjuna* against cadmium-induced oxidant stress and hepatic cell injury via MAPK activation and mitochondria dependent pathway. *Food Chem*. 2010; 123: 1062-1075.
45. Zhang, L., Li, H.Z., Gong, X., Luo, F.L., Wang, B., Hu N., et al. Protective effects of Asiaticoside on acute liver injury induced by lipopolysaccharide/D-galactosamine in mice. *Phytomed*. 2010; 17: 811-819.
46. Wu, Y.L., Lian, L.H.,Wan, Y., Nan, J.X. Baicalein inhibits nuclear factor-_B and apoptosis via c-FLIP and MAPK in d-GalN/LPS induced acute liver failure in murine models. *Chem Biolo Interact*. 2010; 188: 526-534.
47. Zhu,X., Guo, X., Mao, G., Gao, Z., Wang, H., He Q., et al. Hepatoprotection of Berberine Against Hydrogen Peroxide-induced Apoptosis by Upregulation of Sirtuin. *Phytother Res*. 2013; 27: 417-421.
48. Glory, M.D., Thiruvengadam.D. Potential chemopreventive role of chrysin against N-nitrosodiethylamine-induced hepatocellular carcinoma in rats. *Biomed Prev Nutr*. 2012; 2: 106-112.
49. Farombi, E.O., Shrotriya, S., Na, H.K., Kim, S.H., Surh, Y.J. Curcumin attenuates dimethylnitrosamine-induced liver injury in rats through Nrf2-mediated induction of haeme oxygenase-1. *Food Chem Toxicol*. 2008; 46: 1279-1287.
50. Wang, T., Zhao, L.J., Li, P., Jiang, H., Lu, G.C., Zhang, W.D. Hepatoprotective effects and mechanisms of dehydrocavidine in rats with carbontetrachloride-induced hepatic fibrosis. *J Ethnopharmacol*. 2011; 138: 76– 84.
51. Wu, Y., Lin, L., Wen, T., Li, Y.Q. Protective effects of echinacoside on CCl_4-induced hepatotoxicity in rats. *Toxicol*. 2007; 232: 50–56.
52. Kim, S.J., Kim, J.K., Lee, D.U., Kwak, J.H., Lee, S.M. Genipin protects lipopolysaccharide-induced apoptotic liver damage in D-galactosamine-sensitized mice. *Eur J Pharmacol*. 2010; 635: 188–193.
53. Jing, F.Y., Yu, R., Fei, L.P., Ling, D.W., Yin, Z.D., Ling, Z., Genistein protection against acetaminophen-induced liver injury via its potential impact on the activation of UDP-glucuronosyl transferase and antioxidant enzymes. Food Chem Toxicol. 2013; 55: 172–181.
54. Pari, L., Shagirtha, K. Hesperetin protects against oxidative stress related hepatic dysfunction by cadmium in rats. *Exp Toxicol Pathol*. 2012; 64: 513– 520.
55. Farombi, E.O., Shrotriya, S., Surh, Y.J. Kolaviron inhibits dimethyl nitrosamine-induced liver injury by suppressing COX-2 and iNOS expression via NF-κB and AP-1. *Life Sciences*. 2009; 84: 149–155.
56. Kumari, A., Kakkar, P. Lupeol protects against acetaminophen-induced oxidative stress and cell death in rat primary hepatocytes. *Food Chem Toxicol* 2012; 50: 1781–1789.
57. Das, J., Ghosh, J., Roy, A., Sil, P.C. Mangiferin exerts hepatoprotective activity against D-galactosamine induced acute toxicity and oxidative/nitrosative stress via Nrf2–NFκB pathways. *Toxicol Appl Pharmacol*.2012; 260: 35–47.
58. Domitrovic, R., Jakovac, H., Marchesi, V.V., Sain, I., Romic, Z., Raheli, D. Preventive and therapeutic effects of oleuropein against carbontetrachloride-induced liver damage in mice. Pharmacol Res. 2012; 65: 451– 464.
59. Chirdchupunseree, H., Pramyothin, P. Protective activity of phyllanthin in ethanol-treated primary culture of rat hepatocytes. *J Ethnopharmacol*. 2010; 128: 172–176.
60. Xia, D.Z., Zhang, P.H., Fu, Y., Yu, W.F., Ju, M.T. Hepatoprotective activity of puerarin against carbontetrachloride-induced injuries in rats: A randomized controlled trial. *Food Chem Toxicol* 2013; 59: 90–95.
61. Chiu, P.Y., Tang, M.H., Mak, D,H,F., Poon, M.K.T., KO, K.M. Hepatoprotective mechanism of Schisandrin B: Role of mitochondrial glutathione antioxidant status and heat shock proteins. *Free Radical Biol & Med.* 2003; 35: 368–380.
62. Lukivskaya, O., Zavodnik. L., Knas, M., Buko, V. Antioxidant mechanism of hepatoprotection by ursodeoxycholic acid in experimental alcoholic steatohepatitis. *Adv Med Sci*. 2006; 51: 54-59.
63. Pinto, C., Duque, A.L., Galdón, B.R., Cestero, J.J., Macías, P. Xanthohumol prevents carbon tetrachloride-induced acute liver injury in rats. *Food ChemToxicol*. 2012; 50: 3405–3412.
64. Chin, Y.W., Balnus, M.J., Chai, H.B., Douglas, A.K. Drug discovery from natural sources. *AAPS J*. 2006; 8: 239-253.
65. Li, L., Li, W., Kim, Y.H., Lee, Y.W. *Chlorella vulgaris* extract ameliorates carbon tetrachloride-induced acute hepatic injury in mice. *Exp Toxicol Patho*l. 2013; 65: 73–80.
66. Hsu YW, Tsai CF, Chang WH, Ho YC, Chen WK, Lu FJ. Protective effects of *Dunaliella salina* a carotenoids-rich algae, against carbon tetrachloride-induced hepatotoxicity in mice. *Food Chem Toxicol*. 2008; 46: 3311-3317.
67. Lee, M.S., Kim, J.I., Utsuki, T., Park, N.G., Kim, H.R. Cytoprotective effects of phlorofucofuroeckol A isolated from *Ecklonia stolonifera* against tacrine-treated HepG2 cells. *Fitoter*. 2012; 83: 1060–1067.
68. Yeh, Y.H., Hsieh, Y.L., Lee, Y.T., Hu, C.C. Protective effects of *Geloina eros* extract against carbon tetrachloride-induced hepatotoxicity in rats. *Food Research International*. 2012; 48: 551–558.
69. Hwang, H.J., Kim, I.H., Nam, T.J. Effect of a glycoprotein from *Hizikia fusiformis* on acetaminophen-induced liver injury. *Food Chem Toxicol*. 2008; 46, 3475–3481.
70. Bupesh, G., Amutha. C., Vasanth, S., Manoharan, N., Senthil Raja, R., Krishnamoorthy, R., et al. Hepatoprotective efficacy of *Hypnea muciformis* ethanolic extract on CCl_4 induced Toxicity in rats. *Braz. arch. biol. technol*. 2012; 55: 857-863.
71. Esmat, A.Y., Said, M.M., Soliman, A.A., Masry ., Badiea, E.A. Bioactive compounds, antioxidant potential, and hepatoprotective activity of sea cucumber (*Holothuria atra*) against thioacetamide intoxication in rats. *Nutr*. 2013; 29: 258–267.
72. Karthikeyan, R., Somasundaram, S.T., Manivasagam, T., Balasubramanian, T., Anantharaman, P. Hepatoprotective activity of brown alga *Padina boergesenii* against CCl_4 induced oxidative damage in wistar rats. Asian Pac J Trop Med. 2010; 696-701.
73. Raghavendran, H.B., Sathivel, A., Yogeeta, R.S.S.K., Devaki, T. Efficacy of *Sargassum polycystum* (Phaeophyceaee) sulphated polysaccharide against paracetamol induced DNA fragmentation and modulation of membrane bound phosphatases during toxic hepatitis. *Clin Exp Pharmacol and Physiol*. 2007; 34: 142–147.

74. Kumar, K.J.S., Chu, F.H., Hsieh, H.W., Liao, J.W., Li, W.H., Lin, J.C.C., Antroquinonol from ethanolic extract of mycelium of *Antrodia cinnamomea* protects hepatic cells from ethanol-induced oxidative stress through Nrf-2 activation. *J Ethnopharmacol*. 2011; 136: 168–177.
75. Nagaraj, S., Arulmurugan, P., Karuppasamy, K., Jayappriyan, K.R., Sundararaj, R., Vijayanand, N. Hepatoprotective and antioxidative effects of C-Phycocyanin in CCl_4 induced hepatic damage rats. *Acad J Can Res*. 2011; 4: 29-34.
76. Wang, B.S., Lee, C.P., Chen, Z.T., Yud, H.M., Duh, P.D. Comparison of the hepatoprotective activity between cultured *Cordyceps militaris* and natural *Cordyceps sinensis*. *J Func Foods*. 2012; 4: 489-495.
77. Li, B., Lee, D.S., Kang, Y., Yao, N.Q., An, R.B., Ki, Y.C. Protective effect of ganodermanondiol isolated from the Lingzhi mushroom against tert-butyl hydroperoxide-induced hepatotoxicity through Nrf2-mediated antioxidant enzymes. *Food Chem Toxicol*. 2013; 53: 317–324.
78. Wu, S., Yue, Y., Tian, H., Li, Z., Li, X., He, W. Carthamus red from *Carthamus tinctorus* L. exerts antioxidant and hepatoprotective effect against CCl_4 induced liver damage in rats via Nrf2 pathway. *J Ethnopharmcol*. 2013; 148: 570-575.
79. Aniya, Y., Ohtani, I. I., Higa, T., Miyagi, C., Gibo, H., Shimabukuro, M. Dimerumic acid as an antioxidant of the mold, *Monascus anka*. *Free Radical Biol Med*. 2000; 28: 999–1004.
80. Nitha, B., Fijesh, P.V., Janardhanan, K.K. Hepatoprotective activity of cultured mycelium of morel mushroom, *Morchella esculenta*. *Exp Toxicol Pathol*. 2013; 65: 105–112.
81. Soni, B., Visavadiya, N.P., Madamwar, D. Ameliorative action of cyanobacterial phycoerythrin on CCl_4 induced toxicity in rats. *Toxicol*. 2008; 248: 59–65.
82. Jayakumar, T., Ramesh, E., Geraldine, P. Antioxidant activity of the oyster mushroom, *Pleurotus ostreatus*, on CCl_4 induced liver injury in rats. *Food Chem Toxicol* 2006; 44; 1989–1996.
83. Lai, J.T., Hsieh, W.T., Fang, H.L., Lin. W.C. The protective effects of a fermented substance from *Saccharomyces cerevisiae* on carbon tetrachloride-induced liver damage in rats. *Clin Nutr*. 2009; 28: 338–345.
84. Bashandy, S. A., Alhazza, I.M.1., El-Desoky, G. E., Al-Othman, Z. A. Hepatoprotective and hypolipidemic effects of *Spirulina platensis* in rats administered mercuric chloride. *Afr J Pharm Pharmacol*. 2011; 5: 175-182.